Marital status and prostate cancer incidence: a pooled analysis of 12 case-control studies from the PRACTICAL Consortium

Charlotte Salmon[1], Lixin Song[2,3], Kenneth Muir[4,5], UKGPCS collaborators[6], Nora Pashayan[7,8], Alison M. Dunning[8], Jyotsna Batra[9,10], APCB BioResource (Australian Prostate Cancer BioResource)[9,10], Suzanne Chambers[11,12], Janet L. Stanford[13,14], Elaine A. Ostrander[15], Jong Y. Park[16], Hui-Yi Lin[17], Olivier Cussenot[18,19], Géraldine Cancel-Tassin[19,18], Florence Menegaux[20], Emilie Cordina-Duverger[20], Manolis Kogevinas[21,22,23,24], Javier Llorca[25,24], Radka Kaneva[26], Chavdar Slavov[27], Azad Razack[28], Jasmine Lim[28], Manuela Gago-Dominguez[29,30], Jose Esteban Castelao[31], Zsofia Kote-Jarai[32], Rosalind A. Eeles[32,33], on behalf of the PRACTICAL Consortium*, Marie-Élise Parent[1,34]

[1]Epidemiology and Biostatistics Unit, Centre Armand-Frappier Santé Biotechnologie, Institut national de la recherche scientifique, University of Quebec, Laval, QC, Canada

[2]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, US

[3]School of Nursing, University of North Carolina, Chapel Hill, NC, US

[4]Division of Population Health, Health Services Research and Primary Care, University of Manchester, Oxford Road, Manchester, M13 9PL, UK

[5]Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK

[6]http://www.icr.ac.uk/our-research/research-divisions/division-of-genetics-and-epidemiology/oncogenetics/research-projects/ukgpcs/ukgpcs-collaborators

[7]Department of Applied Health Research, University College London, London, WC1E 7HB, UK

[8]Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Strangeways Laboratory, Worts Causeway, Cambridge, CB1 8RN, UK

[9]Australian Prostate Cancer Research Centre-Qld, Institute of Health and Biomedical Innovation and School of Biomedical Sciences, Queensland University of Technology, Brisbane QLD 4059, Australia

[10]Translational Research Institute, Brisbane, Queensland 4102, Australia

[11]University of Technology, Sydney

[12]Cancer Council Queensland, Fortitude Valley, QLD 4006, Australia

[13]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, 98109-1024, USA

[14]Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington 98195, USA

[15]National Human Genome Research Institute, National Institutes of Health, 50 South Drive, Rm. 5351, Bethesda, MD 20892, USA

[16]Department of Cancer Epidemiology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA

[17]School of Public Health, Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA

[18]Sorbonne Universite, GRC n°5 , AP-HP, Tenon Hospital, 4 rue de la Chine, F-75020 Paris, France

[19]CeRePP, Tenon Hospital, F-75020 Paris, France.

[20]Paris-Saclay University, UVSQ, Inserm, Gustave Roussy, CESP, "Exposome and Heredity" team, 94805, Villejuif, France

[21]ISGlobal, Barcelona, Spain

[22]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

[23]Universitat Pompeu Fabra (UPF), Barcelona, Spain

[24]CIBER Epidemiología y Salud Pública (CIBERESP), 28029 Madrid, Spain

[25]University of Cantabria-IDIVAL, 39005 Santander, Spain

[26]Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical University of Sofia, Sofia, 2 Zdrave Str., 1431 Sofia, Bulgaria

[27]Department of Urology and Alexandrovska University Hospital, Medical University of Sofia, 1431 Sofia, Bulgaria

[28]Department of Surgery, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

[29]Genomic Medicine Group, Galician Foundation of Genomic Medicine, Instituto de Investigacion Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, Servicio Galego de Saúde, SERGAS, 15706, Santiago de Compostela, Spain

[30]University of California San Diego, Moores Cancer Center, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA 92093-0012, USA

[31]Genetic Oncology Unit, CHUVI Hospital, Complexo Hospitalario Universitario de Vigo, Instituto de Investigación Biomédica Galicia Sur (IISGS), 36204, Vigo (Pontevedra), Spain

[32]The Institute of Cancer Research, London, SM2 5NG, UK

[33]Royal Marsden NHS Foundation Trust, London, SW3 6JJ, UK

[34]School of Public Health, University of Montreal, Montreal, QC, Canada

* Additional members from the PRACTICAL consortium are provided in the Supplementary Material. Information on the consortium can be found at http://practical.icr.ac.uk/.

Corresponding author: Marie-Elise Parent, PhD

Epidemiology and Biostatistics Unit

Centre Armand-Frappier Santé Biotechnologie

Institut national de la recherche scientifique

Université du Québec

531 boul. des Prairies, Laval (QC), Canada, H7V 1B7

Email: marie-elise.parent@inrs.ca

Telephone: +1-450-686-5676

ABSTRACT

While being in a committed relationship is associated with a better prostate cancer prognosis, little is known about how marital status relates to its incidence. Social support provided by marriage/relationship could promote a healthy lifestyle and an increased healthcare seeking behavior.

We investigated the association between marital status and prostate cancer risk using data from the PRACTICAL Consortium. Pooled analyses were conducted combining 12 case-control studies based on histologically-confirmed incident prostate cancers and controls with information on marital status prior to diagnosis/interview. Marital status was categorized as married/partner, separated/divorced, single, or widowed. Tumours with Gleason scores ≥8 defined high-grade cancers, and low-grade otherwise. NCI-SEER's summary stages (local, regional, distant) indicated the extent of the cancer. Logistic regression was used to derive odds ratios (ORs) and 95% confidence intervals (CI) for the association between marital status and prostate cancer risk, adjusting for potential confounders.

Overall, 14,760 cases and 12,019 controls contributed to analyses. Compared to men who were married/with a partner, widowed men had an OR of 1.19 (95%CI 1.03-1.35) of prostate cancer, with little difference between low- and high-grade tumours. Risk estimates among widowers were 1.14 (95%CI 0.97-1.34) for local, 1.53 (95%CI 1.22-1.92) for regional, and 1.56 (95%CI 1.05-2.32) for distant stage tumours. Single men had elevated risks of high-grade cancers.

Our findings highlight elevated risks of incident prostate cancer among widowers, more often characterized by tumours that had spread beyond the prostate at the time of diagnosis. Social support interventions and closer medical follow-up in this sub-population are warranted.

Keywords: Marital status, Prostate cancer, Consortium, Pooled analysis, Meta-analysis

DECLARATIONS

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The PRACTICAL consortium

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Conflict of interest/Competing interests

The authors declare that they have no conflict of interest.

Availability of data and material

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Code availability

Available from the authors on request.

Authors' contributions

CS conducted the analysis and prepared the manuscript. MEP supervised the work, participated in the conception of the study, and reviewed the manuscript. All authors participated in the interpretation of data, and provided important intellectual contributions to the manuscript.

Ethics approval

All individual studies were approved by local ethics committees and adhered to the principles of the Declaration of Helsinki.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable

INTRODUCTION

Prostate cancer is one of the most common cancers in men worldwide, and a leading cause of cancer death [1]. Its etiology remains poorly understood. The only risk factors clearly identified are age, ancestry, a family history of prostate cancer, and some 270 genetic susceptibility variants estimated to explain about one-third of the familial relative risk [2, 3]. None of these factors is modifiable, precluding the establishment of preventive strategies.

Striking geographic variations in incidence, which cannot be fully explained by detection practices [4], and evidence from migration studies [5] suggest that exogenous factors such as environmental and lifestyle factors likely play a role in its development. Around 40% of prostate cancer etiology would be explained by exogenous factors [6]. Underlying circumstances affecting behavior, such as marital status, could thus influence prostate cancer development.

There is fairly consistent epidemiological evidence of an association between marital status and health [7, 8]. Being in a committed relationship has been found to be globally associated with a healthier lifestyle, such as less smoking and alcohol consumption, better diet, more physical activity, and with maintaining a healthy body weight [9-12]. As these factors are suspected to contribute to prostate cancer risk [2], they may explain, at least in part, an association between marital status and risk of this cancer. Moreover, social support provided by marriage may play a stress-buffering role, and motivate maintaining these healthy lifestyle behaviors [13]. Conversely, because women are more likely to engage in regular health care such as preventive care visit (i.e., screenings), for

themselves and their family members [14, 15], marriage could increase the likelihood of screening and earlier detection of disease among spouses [16, 17].

Most in-depth investigations of the association between marital status and prostate cancer have focused on cancer prognosis rather than incidence. Findings suggest that unmarried men have a higher risk of adverse prostate cancer outcomes and mortality [18-20]. This has raised the possibility that widowers might benefit from routine screening [21]. Results from the handful of studies reporting on incidence are inconsistent [22-32], and to our knowledge, none has examined relationships with cancer grade at diagnosis. Moreover, studies to date should be interpreted with caution as in many, observations were hampered by small sample sizes and limited statistical power [22, 26, 27, 31], or presented no adjustment [24, 30, 32]. Finally, there was heterogeneity in the definition of marital status and of prostate cancer stages across studies, making comparison across studies difficult.

We present here evidence on the association between marital status and risk of incident prostate cancer, overall and by cancer grade and stage, using data from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium.

METHODS

Study Population

The study population included subjects integrated in the PRACTICAL consortium, a large international collaborative group established in 2008 which has assembled a large amount of genetic and epidemiologic data from multiple prostate cancer studies, with a primary aim to identify genetic risk factors. PRACTICAL currently consists of 133 study groups, including clinical trials, case-control and cohort studies, distributed all around the world, mostly in Europe and North America. A detailed

description of the study groups is available at http://practical.icr.ac.uk. All individual studies were approved by local ethics committees and adhered to the principles of the Declaration of Helsinki.

Overall, 57 studies agreed to contribute their data to the present analysis. We excluded 34 studies that had more than 90% missing data on marital status, or that did not have information on it, for either all cases or all controls. Cohort studies typically had information on marital status at baseline, without further updates in status. To avoid heterogeneity due to differences in study design and timing of collection of marital status information, only case-control studies were selected. As a result, analyses were conducted on data from 12 case-control studies.

Exposure

Epidemiologic data were provided in accordance with the pre-established PRACTICAL data dictionary. Marital status was classified as married/partner, divorced/separated, single (i.e., never married), or widowed at prostate cancer diagnosis or interview (index date). For all analyses, individuals identified as married/with a partner constituted the reference category.

Outcome

Cases were men newly diagnosed with primary, histologically-confirmed invasive prostate cancer. Controls were men with no history of prostate cancer, frequency-matched to cases on age, ancestry and geographical region.

The degree of aggressiveness of prostate cancer was defined using the Gleason score, which reflects cell differentiation [33]. Following a recent recommendation [34], a tumour with a Gleason score ≥ 8 was considered as high-grade [35] whereas a score ≤ 7 indicated a low-grade cancer. We also used an alternate definition of high-grade tumours (Gleason scores ≥7 [4 + 3]) [35], but as results were similar to those based on scores ≥ 8, only the latter are presented here.

According to the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute [36], cancer stage was defined as local when the cancer was confined to the prostate, regional if there was direct extension involving adjacent local structures and local lymph nodes, and distant for direct extension beyond local structures or metastasis.

Covariates

Potential confounders, identified using a directed acyclic graph (DAG, Supplementary Fig.1), were age at diagnosis for cases or at interview for controls (modelled as continuous, after confirming the linearity of the logit), and ancestry (European, African, Asian and other). Additional variables, not retained in the DAG but used to describe the study population, included first-degree family history of prostate cancer (no, yes), education (none, primary or secondary school, university degree, and professional qualification), overall physical activity from either occupation or leisure activities (low activity or sedentary, moderate activity, high or energetic activity), current alcohol intake (no, yes), smoking status (never smoker, ex-smoker, current smoker), and current or recent body mass index (BMI) in kg/m^2.

Statistical analyses

Pooled analysis

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between marital status and prostate cancer risk, combining data of individual participants from the 12 studies. Polytomous models were fitted to examine associations separately by cancer stage (local, regional, and distant compared to controls) and aggressiveness (low- and high-grade, compared to controls). Cases were excluded from the analyses by cancer stage and grade (27% and 12%, respectively) in the event of corresponding missing information. Sub-

analyses were conducted to evaluate whether associations with marital status varied according to ancestry.

In order to take into account potential heterogeneity among studies and inherent confounding effects, all analyses were adjusted for individual study sites in addition to the potential confounding factors identified by the DAG (age and ancestry). Results based on a minimal model adjusting only for age and study (data not shown) were virtually the same as those based on the fully adjusted model.

Overall, 2.8% of subjects had missing data on at least one of the covariates included in the model (0.8% for age, 2.0% for ancestry). Assuming that missing data were missing at random, multiple imputations were performed using three imputed data sets [37]. No imputation was performed for the marital status variable and only subjects with such information were included.

In order to evaluate the impact of missing data on marital status, we also performed analyses excluding studies having more than 25% of missing values for marital status. Finally, to evaluate the robustness of our findings to residual confounding, we calculated E-values [38], which indicate the minimum strength of association that an unmeasured confounder would need to have to explain away the associations observed in the pooled analysis.

Meta-analysis

We performed a meta-analysis for the association between marital status and overall prostate cancer risk to visualize study-specific results, and to explore study heterogeneity. Study-specific risk estimates were derived using multivariable unconditional logistic regression models. Age-adjusted summary ORs and 95% CIs were assessed by a random effect model using the DerSimonian and Laird method[39]. Tests of heterogeneity between studies were performed using the Cochran's Q test and the index of consistency I^2 statistics. A p-value of the Cochran's Q test < 0.1 was considered to be

indicative of heterogeneity. Observed values of I^2 between 30% and 60%, 50 and 90% and 75% and 100%, suggested moderate, substantial and considerable heterogeneity, respectively [40].

A subgroup meta-analysis was performed, restricted to studies with less than 25% of missing values for marital status.

All analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Case-control studies characteristics

Characteristics of the 12 studies included in the analyses are displayed in Supplementary Table 1. The majority were conducted in Europe (two in the United Kingdom, two in Spain, two in France and one in Bulgaria). Two studies took place in the United States, and one each in Canada, Australia and Malaysia.

Subjects' characteristics differed slightly among studies. The mean age of participants ranged from 59.5 years to 68.6 years. All studies included a majority of subjects of European ancestry, except for the Malaysian study where nearly all subjects were of Asian descent. The most common marital status category at index date across studies was "married/with a partner".

Study population

The study population for analysis consisted of 14,760 cases and 12,019 controls with complete information on marital status. The mean age at diagnosis was 62.6 years for cases (standard deviation [sd] = 7.1) and 60.4 years at interview for controls (sd=7.7) (Table 1). Most individuals were of European ancestry. Cases were more likely than controls to be of African ancestry and to have a

first-degree family history of prostate cancer (age-adjusted ORs = 1.89; 95% CI = 1.61-2.23 and 1.85; 95% CI = 1.71-1.99, respectively). A higher proportion of cases than controls had no education, primary or secondary school levels, or a university degree, although education was missing for a substantial number of controls. Overall physical activity level and alcohol intake distributions were fairly similar between cases and controls. Compared to controls, cases had a higher proportion of ex-smokers and a slightly higher mean BMI.

Overall, 82.7% of cases and 83.1% of controls were married or with a partner. About 7.3% of study subjects were separated/divorced, and 5.3% were single, with little differences between cases and controls. Cases were more often widowers (5.1%) than controls (3.7%).

Pooled analysis of marital status and prostate cancer risk

Table 2 shows the ORs for the association between marital status and the risk of prostate cancer overall, and by cancer stage and grade. As compared to men who were married/with a partner, widowed men had a higher risk of prostate cancer overall (OR = 1.19; 95% CI = 1.03-1.35) while those who were separated/divorced or single had a similar risk of the disease.

In analyses focusing on tumour stage at diagnosis, widowhood was associated with an OR of 1.14 (95%CI 0.97-1.34) of a local stage, of 1.53 (95%CI 1.22-1.92) of a regional stage, and of 1.56 (95% CI = 1.05-2.32) of a distant stage prostate cancer. There was no evidence that separated/divorced men and single men had different odds of cancer stages than those who were married/with a partner.

When considering tumour grades, widowed men had similarly increased odds of low- and high-grade tumours. For single men, we observed a 21% increase in odds of being diagnosed with a high-grade tumour, compared to those married/with a partner (1.21; 95% CI = 1.00-1.50). Risk estimates were comparable between men separated/divorced and those who were married/with a partner.

Analyses using complete sets of data, without imputations for covariates, yielded similar results (data not shown).

Supplementary table 2 presents associations between marital status, distant stage at diagnosis and high-grade tumours, according to the main ancestry groups. While risk estimates were imprecise owing to small numbers, there were suggestions of increased risk of distant stage cancers among widowers and of high-grade cancers among single men of European descent. Associations were particularly strong for widowers of Asian descent, in particular for distant stage and high-grade tumours, while no relationships emerged for men of African ancestry.

When restricting analyses to the six studies with less than 25% of missing values for marital status (median=1.8%), including 9,459 cases and 6,770 controls, results were consistent with those based on the full sample, with elevated risks of distant stage cancers among widowers and of high-grade tumours among single men (Table 3).

Based on E-value estimations, an unmeasured confounder would have to be related to both exposure and outcome according to an OR of 1.67 each (E-value for the lower 95% CI = 1.21) to fully explain the observed odds ratio of 1.19 for widowed men in the pooled analysis. The E-value was higher when considering distant stage (estimate = 2.49; lower 95% CI = 1.28). For single men, the E-value was 1.74 for high-grade prostate cancer (lower 95% CI = 1.16).

Meta-analysis

Forest plots of study-specific ORs and 95% CI for the association between marital status and prostate cancer risk are shown in Figures 1-3.

The meta-OR for overall prostate cancer across the 11 studies from which an association among widowed men could be estimated was 1.19 (95% CI = 0.79-1.78). However, substantial to considerable heterogeneity was detected (Q=70.77, p<0.001, I^2=86%) (Fig.1). In accordance with findings from the pooled analyses, we observed an increased risk of diagnosis at a more advanced disease stage among widowers, with a random effect summary OR of 1.15 (95% CI = 0.69-1.91) for

local, 1.46 (95% CI = 1.04-2.03) for regional, and 1.73 (95% CI = 0.97-3.09) for distant stage. Corresponding heterogeneity levels, based on I^2 values, were high for local stage, but low to moderate for regional and distant stage cancers.

Separated/divorced men showed no elevation in odds of being diagnosed with prostate cancer, overall and according to cancer stage and grade (Fig.2). The overall random effect summary OR was 1.06 (95% CI = 0.95-1.19) for overall prostate cancer, with no evidence of heterogeneity among the 10 studies which had collected information on this status (Q=9.39, p=0.40, I^2=4%).

For single men, 10 studies were included, in which substantial heterogeneity was detected (Q=24.39, p=0.004, I^2=63%) (Fig.3). The random effect summary OR for overall prostate cancer was 0.96 (95% CI = 0.76-1.22), suggesting no association, although risks of high-grade tumours were somewhat elevated (OR = 1.22, 95% CI = 0.77-1.92).

After restricting the meta-analysis to studies with less than 25% of missing values for marital status, results similar to those in the main analysis were found, with globally less heterogeneity between studies (Supplementary Tables 3 and 4). An elevated risk of overall prostate cancer was observed among widowed men (random effect summary OR = 1.31, 95% CI = 1.00-1.72, Q=7.75, p=0.1708, I^2=36%). In analyses focusing on cancer stage, widowhood was associated with a random effect summary OR of 1.40 (95%CI 0.97-2.02) for local stage, of 1.55 (95%CI 0.97-2.48) for regional stage, and of 2.46 (95% CI = 1.05-5.78) for distant stage. Moreover, as observed in the pooled analysis, elevated risks of high-grade cancers were found among single men, with a random effect summary OR of 1.89 (95% CI = 1.09-3.28).

DISCUSSION

Our overall findings show that widowers had elevated risks of being diagnosed with prostate cancer, particularly with tumours that had spread at the time of detection. To our knowledge, our study is

the first to have investigated specifically the association between marital status and prostate cancer grade at diagnosis. Single men were found to be at increased risk of high-grade prostate cancer. By contrast, there was no evidence that separated/divorced men had higher risk of prostate cancer than men who were married/with a partner. Results were consistent across pooled, meta- and sensitivity analyses.

Associations between marital status and prostate cancer incidence have been reported previously. However, in the vast majority of reports, marital status was not the main focus of the analyses [22-24, 26, 29, 32] and was presented as an ancillary result, without an in-depth investigation. Most studies observed that men who were not married had lower risks than those who were married [22, 25, 26, 29, 30, 32]. In particular, a nationwide population-based case-control study conducted in Sweden observed a 31% increased risk of developing prostate cancer among married men, compared to those who were never married (OR = 1.31; 95% CI = 1.29-1.33)[32]. This elevation in risk was largest for low-risk prostate cancer (based on stage, grade and prostate-specific antigen (PSA) level), leading to the interpretation that these findings might reflect a higher uptake of PSA testing among married men. Conversely, a few studies reported no association with marital status [23, 27, 28, 31]. Only one study, conducted in Alberta, Canada, suggested an increased risk of overall prostate cancer among never married men (OR = 1.93; 95% CI = 1.08-3.44), while no association emerged for separated, divorced or widowed men [24].

A recent systematic review investigated the association between marital status and cancer stage at diagnosis across several cancer sites [41]. Of the three studies reporting on prostate cancer, two found a decreased risk of presenting with metastatic disease or advanced stage among married men compared to unmarried men, and one reported an increase of locally advanced prostate cancer among separated, divorced, or widowed men. Findings for widowers concur with ours.

Marriage or partnership can affect prostate cancer risk through different pathways. It is one of the most important sources of emotional support and social interaction. Being in a committed

relationship has been found to be related with a healthier diet, less smoking and alcohol consumption [9, 13], which may relate to prostate cancer risk [2]. Moreover, married men are more likely to adopt and maintain healthy behaviors as marriage and its symbolic meaning is accompanied by a sense of responsibility and norms that increase their will to stay healthy in order to take care of their family members [42]. Social support provided by marriage can also influence health outcomes through stress-buffering mechanisms. It increases the ability to cope with stress by providing the needed material and psychological resources and therefore reduces the negative effects of stressful events, such as the adoption of unhealthy lifestyle behaviours and the activation of physiological responses detrimental to health [43].

In our study, widowed men had a higher risk of prostate cancer than single or separated/divorced men. This may reflect the emotional impact of widowhood and its related health effect. The "widowhood effect" or the increased risk of mortality, including from cancer, among widowed persons compared with those who remain married is well documented [44]. Explanations include what is called the selection effect into widowhood, which makes widowers more likely to die or to develop disease because of shared household characteristics and behaviours with the lost one, the direct effect of the psychological shock, and lifestyle modifications accompanied by widowhood [45, 44].

We found that widowed men were more likely than those who were married/with a partner to be diagnosed at a more advanced stage. This is in line with the notion that marriage promotes health seeking behaviors which increase the likelihood to be diagnosed at an earlier stage of the disease, because women are more likely to seek regular care, such as screenings, for themselves and their husband [14, 46]. This is supported by a recent study, which suggests that married/with a partner men are more likely than never married, divorced, separated, or widowed men to undergo screening and prostate biopsy [47]. Without the encouragement of a spouse to seek medical attention, cancer

in widowed men may remain undetected and diagnosis can be delayed, leading to a more advanced disease and poorer prognosis.

For single men, we observed different odds ratios according to cancer grade. The latter appears to differentiate early in the carcinogenesis process, with no evidence of direct progression from low- to high-grade prostate cancers [48]. This suggests that low- and high-grade prostate cancers may have different etiologies and sets of risk factors. This is supported by findings where risk factors varied according to cancer grade [49, 50]. It may thus be that the underlying etiological factors behind marital status are associated with different prostate cancer grades.

We are not aware of previous studies investigating associations between marital status and prostate cancer incidence across ethnic groups. Albeit based on limited numbers, our findings are suggestive of elevated risks of distant stage and high-grade cancers among widowed and single men of European descent. These risks were particularly pronounced for men of Asian descent, but not among men of African ancestry. Cultural differences in reaching out for regular medical follow-ups, in the absence of a partner providing social support, might explain these observations.

This study presents some limitations. First, a sizable proportion of cases (52%) and controls (32%) in the 12 studies included had missing information on marital status (Supplementary Tables 5 and 6). In order to evaluate whether their exclusion from the analyses could have resulted in selection bias, we compared study participants and those excluded for lack of information. Subjects without marital status information tended to have a slightly higher BMI, to smoke and to have more often a family history of prostate cancer, but they were less likely to have received no education. However, within the sample of subjects with complete information, none of these variables was associated with marital status. Furthermore, restricting analyzes to studies with less than 25% of missing data for marital status reduced heterogeneity across studies and reinforced findings for widowers (distant cancers) and single men (high-grade cancers). These observations provide reassurance against selection issues operating in the study and explaining our findings. An additional indicator of the

comparability of our study population to others comes from our replication of higher risks, in a similar order of magnitude, of prostate cancer among men of African descent and those with a first-degree family history of the disease.

Secondly, even if we adjusted for the specific study contributing to the pooled analyses, we cannot rule out that the observed associations could have been explained, at least in part, by the heterogeneity among studies. This could reflect variation in terms of study population, healthcare access and screening practices, recruitment of participants and assessment of exposures. However, our meta-results, taking into account study heterogeneity using a random effect model, generated results that were consistent with those from the pooled analyses. Furthermore, heterogeneity was lower in our sub-analysis of studies with fewer missing values for marital status and the overall interpretation of findings was unaltered.

Another limitation relates to errors inherent in the studies included in the analyses, such as a possible misclassification of reports on marital status, although we would expect reporting error to be non-differential between cases and controls, attenuating the associations observed. Moreover, the duration of the marital status captured at diagnosis/interview was not known.

Information on screening practices was not available, hampering our ability to evaluate the possible underlying role of screening in our findings. Nevertheless, a stratified analysis according to study countries, which may serve as a crude proxy for screening practices, suggested no difference in the results (data not shown).

Finally, the data at hand had too sparse information to conduct formal mediation analyses to identify the causes behind the associations observed.

Our study has several strengths. The PRACTICAL consortium is a unique resource for identifying risk factors that can be related to prostate cancer risk by combining a large amount of data from many studies. Inclusion of 14,760 prostate cancer cases and 12,019 population controls provided high

statistical power and the ability to effectively investigate associations with cancer stage and grade. In addition, we made a comprehensive assessment of potential confounders using a DAG, although none emerged here as particularly important. Through the E-value, we estimated the strength of association that an unmeasured factor would require to explain away the association that we observed [38]. The results suggest that relatively weak confounder associations could explain some of the results. Thus, residual confounding by unmeasured confounders is possible, although few risk factors for prostate cancer have yet been clearly identified. Our ability to conduct several sensitivity analyses confirmed the robustness of our findings.

CONCLUSION

In this analysis of 12 case-controls studies, we found an increased risk of prostate cancer among widowed men, more often characterized by tumours that had spread at the time of diagnosis. Single men had greater risks of high-grade cancers. Future studies based on variations of marital status over time, considering ethnic sub-groups as well as screening practices, are indicated. Moreover, it would be of interest to perform a causal mediation analysis to better understand the possible underlying role of lifestyle and other factors. Should the current results be confirmed, they can provide new insights for prostate cancer prevention by targeting vulnerable populations, such as widowed men, and reducing health disparities through social support intervention.

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FIGURE LEGENDS

Fig.1 Forests plot of studies comparing widowed men to those who are married or with partner, overall (a) and according to cancer grade (b) and stage (c)

Fig.2 Forest plots of studies comparing separated and divorced men to those who are married or with partner, overall (a) and according to cancer grade (b) and stage (c)

Fig.3 Forests plot of studies comparing single men to those who are married or with partner, overall (a) and according to cancer grade (b) and stage (c)